REMARKS

Claims 144-156, 159-170, 177, 179 and 183-185 presently appear in this case. No claims have been allowed. The official action of November 28, 2003, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to a method for identifying continuous peptides that simulate a discontinuous epitope of a single biological unit, i.e., that interact with a ligand that interacts with a discontinuous epitope of a single biological unit. The single biological unit may be a protein or a complex of proteins. The DNA that encodes the amino acid sequence of the biological unit is divided into DNA fragments. A library of oligonucleotides is then created, each comprising at least two of such fragments that are randomly ligated. Preferably, the random ligation is such that any oligonucleotide in the library can ligate with any other oligonucleotide in the library. Preferably, this library will contain oligonucleotides of fragment pairs in which each fragment is linked to each other fragment. The oligonucleotides are inserted into an expression system and then expressed. The resultant is then screened for interaction with a ligand that interacts with a discontinuous epitope of the single biological unit. Those that are

identified with such positive interaction are then produced and can serve to simulate the native discontinuous epitope.

The interview between Examiner Fredman and the undersigned attorney conducted on March 24, 2004, is hereby gratefully acknowledged. In the interview, the undersigned explained why the present claims did not read on the processes of Huse, either alone or in combination with the secondary references. Additionally, wording was discussed which, if placed in the claims, would further differentiate the process of the present invention from Huse and Stemmer. The arguments presented at the interview will appear in the discussion of the rejection herein.

Claims 157, 158, 171-176, 178 and 180-182 have been withdrawn from consideration. All of these claims have now been deleted without prejudice toward the continuation of prosecution thereof in a divisional application.

Claims 144-151, 154-156, 159-165 and 168-170 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Huse in view of Stemmer. Regarding claim 144, the examiner states that Huse discloses a method of identifying and producing a peptide that interacts with a ligand that interacts with a discontinuous epitope of an antibody by providing a plurality of DNA fragments that appear in a DNA sequence encoding the antibody; creating a library of

oligonucleotides comprising at least two randomly ligated DNA fragments; inserting each of said oligonucleotides into a phage; expressing the peptides encoded by the oligonucleotides; screening the expressed peptides for interaction with a ligand that interacts with a discontinuous epitope (i.e., an antigen); and identifying the peptide and producing the identified peptide. The examiner acknowledges that Huse does not teach applying the method to a single gene. The examiner interprets the statement that the plurality of DNA fragments consists of fragments from a single biological unit as limiting the claim to a single gene. The examiner states, however, that Stemmer teaches the use of a single gene, referring to the statement at column 16, lines 15-18, about mutagenesis (including shuffling) of a single antibody gene. The examiner states that example 8 clearly shows the application of the shuffling to a single antibody gene, and example 9 applies the method to the B-lactamase gene. The examiner considers that it would have been *prima facie* obvious to modify the method of Huse to apply the analysis to a single biological unit such as a single gene because Stemmer expressly teaches the desirability of using single genes. This rejection of claim 144 is hereby respectfully traversed.

On pages 15 and 16 of the official action, in response to applicant's previous arguments, the examiner

states that applicant's entire argument relied upon a particular definition of the phrase "single biological unit", but that the examiner considers the antibody of Stemmer to be a single biological unit. However, applicant has never argued that an antibody was not a single biological unit. Applicant argued at page 4 of the response of October 2, 2003:

> However, once a single antibody gene is subjected to mutagenesis, it is no longer a single biological unit. Each mutant is a separate biological unit.

It more accurately should have said that the single biological unit in Stemmer is an antibody, not an antibody gene. The DNA that encodes the parent antibody is mutated. Each mutant DNA sequence encodes a separate biological unit. Thus, the DNA being shuffled in Stemmer does not encode a single biological unit regardless of whether or not it originates from a single gene.

It is apparently the examiner's position that the plurality of mutated DNA molecules of Stemmer, each of which encodes a different antibody, can be interpreted as "a single type of biological molecule" or as "a functional recitation of a molecule which functions in a biological way." However, this language does not appear in the claim.

At the interview, the examiner indicated that he still was not convinced that the plurality of mutated antibody chains could not broadly be considered to fall within the term

"a single biological unit" as used in claim 144. The examiner agreed, however, that there were substantial differences in the disclosed process of the present invention and those of Huse and Stemmer, as it is not an object Huse or Stemmer to find peptides that interact with a ligand that interacts with a discontinuous epitope of a single biological unit, as is the broad concept of the present invention. Additionally, neither Huse nor Stemmer breaks the DNA encoding the single biological unit into a plurality of small fragments that are then ligated randomly to form a plurality of small ligated fragments that are then tested for binding to the ligand that binds to a discontinuous epitope of the original molecule. Furthermore, Huse and Stemmer do not randomly ligate in the sense that it is possible for any oligonucleotide to ligate with any other oligonucleotide in the library. In Huse and Stemmer, the oligonucleotides must ligate in a very specific order in order to maintain the antibody activity of the final product. Furthermore, in the present invention it is preferred that the single biological unit have a single definable sequence or, if it consists of two or more proteins that interact to form a complex, that each of the proteins have a single definable sequence. Furthermore, in Huse, a complete set of DNA fragments is not produced, while these may be produced in the present invention. Another difference is that in the

screening step, the molecules being screened are functional antibody molecules in Huse and Stemmer, while it is preferred that the ligated fragments being screened in the present invention are substantially smaller than that and never reconstitute the original single biological unit. The examiner suggested in the above-mentioned interview that independent claims be presented to one or more of these possible means of distinguishing the present invention from Huse and Stemmer.

Claim 144 has now been amended to insert language relating to one of the methods discussed in the interview to potentially differentiate from Huse and Stemmer. In step (b) of claim 144, the term "randomly ligated" is further defined by adding the phrase "such that any oligonucleotide in the library can ligate with any other oligonucleotide in the library". This defines over both Huse and Stemmer, as neither reference discloses any process with such a truly random ligation. In both Huse and Stemmer, it is not possible for every oligonucleotide in the library to ligate with every other oligonucleotide in the library, as it critical that the oligonucleotides ligate in a specific order. Again, reference is made to column 16, lines 41-43, of Stemmer, where it states:

> Further, shuffling conserves the relative order, such that, for example, CDR1 will not be found in the position of CDR2.

In Huse, separate heavy and light chain libraries were constructed containing all of the different light chains that may appear in a parent animal. Thus, as stated in the first column on page 1277, the initial Fab expression library was constructed from mRNA isolated from a mouse that had been immunized with the NPN antigen. By PCR amplification, a library of light chain vectors was prepared, each containing a light chain obtained from this mRNA, and library of heavy chain vectors was obtained, each containing a heavy chain fragment from this mRNA (see Fig. 1 at page 1276). Then a combinatorial construct containing a random combination of one of the light chains in the library with one of the heavy chains in the library was prepared. The term "random" is used in the last full paragraph of the second column of page 1277, but it can be seen from context that this means that each light chain is randomly selected from the light chain library and each heavy chain fragment is randomly selected from the heavy chain library, so that the actual combinatorial construct of the V_H and V_L is a random combination of the two. However, because of the antisymmetric placement of restriction sites in the linear vector (see the paragraph bridging pages 1276 and 1277), the resulting combinatorial construct has a

fixed sequence and order, with the heavy chain always upstream of the light chain.

It cannot be said that every oligonucleotide in the library of Huse can ligate with every other oligonucleotide in the library. Indeed, members of the light chain library cannot ligate with one another and members of the heavy chain library cannot ligate with one another. Furthermore, they must end up not in a random sequence, but in a very fixed and formal sequence, so that the resulting library will be a population of functional antibody fragments (Fab's) (see the first full paragraph on page 1276).

It is very clear from the procedure described in Example 5 beginning at page 30 of the present specification, and particularly the last full paragraph on page 31 of the present specification, that any two of the resulting fragments can ligate to one another in the present process, thus providing support for the present claim language. As present claim 144 now clearly defines over the processes of Huse and Stemmer, reconsideration and withdrawal of this rejection are respectfully urged.

If the independent claim is no longer subject to the rejection, then all of the dependent claims must also be allowable. Accordingly, reconsideration and withdrawal of the

rejections of all of the claims dependent from claim 144 is also respectfully urged.

The same amendment has also been made to independent claim 159. Thus, claim 159 and those claims dependent therefrom are also free of this rejection for the same reasons as discussed above with respect to claim 144. Reconsideration and withdrawal of the rejection of these claims is also respectfully urged.

Claims 152, 153, 166, and 167 have been rejected as being unpatentable over Huse in view of Stemmer and further in view of Marks. This rejection is also respectfully traversed.

Marks, like Huse and Stemmer, requires that the final product have functional antibody activity. Thus, like Huse and Stemmer, the fragments cannot be randomly ligated such that any oligonucleotide in the library can ligate with any other oligonucleotide in the library. The fragments must ligate in a very specific manner to get a specific final product. Thus, Marks adds nothing to the deficiencies of Huse and Stemmer relating to the independent claims 144 and 159. Accordingly, those dependent claims subject to the present rejection must be allowable for the same reasons as the independent claims from which they depend. Reconsideration and withdrawal of this rejection is therefore also respectfully urged.

New claim 183 has now been added which is identical to previously appearing claim 144, but which adds to step (e) the feature that none of the expressed peptides being screened are the original single biological unit. This defines over Huse and Stemmer, because both of those references end up with a library of functional antibodies, or functional antibody fragments, which are the same as the single biological unit as originally defined by the examiner. With the present invention, it is the fragments that are being screened. That which is screened are the ligated fragments. As one is looking for an epitope, such ligated fragments will never be as large as the original biological unit. Thus, this feature also defines over Huse, Stemmer and Marks. Accordingly new claim 183 should also be found to be allowable.

New claim 184 has also now been added, which is the same as previously appearing claim 144, but in which the first paragraph is amended to specify that the single biological unit consists of a protein "having a single definable sequence" or consists of two or more proteins "each having a single definable sequence". This language is intended to define over the somewhat questionable interpretation of the examiner that a plurality of mutated sequences, which all have antibody activity, can be interpreted to be a single biological unit. Claim 184 makes explicit that a single

biological unit must have a single definable sequence. Note that the second paragraph of Example 5 on page 30 of the present specification specifies that in a preferred emodiment, the single biological unit is obtained by cutting out a portion of the genome of an organism. This will necessitate that that portion have a single definable sequence. Thus, this language is inherent in the specification as filed. Accordingly, it is urged that new claim 184 defines over the references of record in its own right and should also be considered to be allowable in this case.

New claim 185 has also now been added, which is the same as previously appearing independent claim 159, but with the same amendment to the first paragraph as in new claim 184 discussed above. Thus, new claim 185 defines over the prior art for the same reasons as discussed above with respect to claim 184.

It is submitted that all of the claims now present in the case clearly define over the references of record and fully comply with 35 U.S.C. §112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

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